NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC)
GUIDELINE SYNTHESIS

SCREENING FOR CERVICAL CANCER

Guidelines

1. American Cancer Society (ACS). American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin 2002 Nov-Dec;52(6):342-62. [88 references]
2. Brigham and Women's Hospital (BWH). Cervical cancer: screening recommendations, with algorithms for managing women with abnormal Pap test results. Boston (MA): Brigham and Women's Hospital; 2004 Dec. 11 p. [11 references]
3. New Program in Evidence-based Care (PEBC). Cervical screening. Toronto (ON): Cancer Care Ontario (CCO); 2005 May 20. 39 p. [74 references]
4. University of Michigan Health System (UMHS). Adult preventive health care: cancer screening. Ann Arbor (MI): University of Michigan Health System; 2004 May. 12 p. [4 references]
5. United States Preventive Services Task Force (USPSTF). Screening for cervical cancer: recommendations and rationale. Am Fam Physician 2003 Apr 15;67(8):1759-66. [32 references]

TABLE OF CONTENTS

INTRODUCTION

A direct comparison of the American Cancer Society (ACS), Brigham and Women's Hospital (BWH), Program in Evidence-based Care (PEBC), University of Michigan

Health System (UMHS), and United States Preventive Services Task Force (USPSTF) recommendations for cervical cancer screening is provided in the tables below. The guidelines differ somewhat in scope. In addition to general screening recommendations, ACS and BWH consider methods for collecting the Pap smear sample. BWH also addresses classification of Pap smear results, follow-up treatment, and the tracking and reporting of screening results. ACS addresses the need to educate women about gynecologic care, pelvic and rectal exams, referrals for women with low grade-lesions, and health insurance issues. PEBC includes recommendations for screening women with special circumstances (immunocompromised or human immunodeficiency virus (HIV) positive women, pregnant women, and women who have sex with women) and for managing women with abnormal cytology. All of the guidelines consider the role of new screening technologies, such as liquid-based Pap technology and human papillomavirus (HPV) testing. In formulating their recommendations, BWH, PBEC, and UMHS reviewed the conclusions of USPSTF and ACS.

Table 1 compares the scope of each of the guidelines. Table 2 compares recommendations concerning whom to screen, screening women with a hysterectomy, screening tests and testing frequency, and new screening technologies. Table 3 compares the potential benefits and harms associated with the implementation of each guideline.

The level of evidence supporting the major recommendations in the guidelines is also identified, with the definitions of the rating schemes used by ACS, PEBC, UMHS, and USPSTF included in Table 4.

Following the content comparison tables, the areas of agreement and differences among the guidelines are identified.

Abbreviations used in the text and tables follow:

- ACS, American Cancer Society
- ASC-US, atypical squamous cells -- uncertain significance
- ACOG, American College of Obstetricians and Gynecologists
- BWH, Brigham and Women's Hospital
- CIN, cervical intraepithelial neoplasia
- DES, diethylstilbestrol
- DNA, deoxyribonucleic acid
- FDA, U.S. Food and Drug Administration
- HIV, human immunodeficiency virus
- HPV, human papillomavirus
- HSIL, high-grade squamous intraepithelial lesion
- LBP, liquid-based Pap
- LSIL, low-grade squamous intraepithelial lesion
- NCCN, National Comprehensive Cancer Network
- Pap, Papanicolaou
- PEBC, Program in Evidence-based Care
- STD, sexually transmitted disease
- UMHS, University of Michigan Health System
- USPSTF, United States Preventive Services Task Force

TABLE 1: COMPARISON OF SCOPE AND CONTENT	
Objective and Scope	
ACS (2002)	• To update the 1988 American Cancer Society guideline pertaining to early detection of cervical neoplasia and cancer • To offer new screening recommendations that address when to begin screening, when screening may be discontinued, whether to screen women who have had a hysterectomy, appropriate screening intervals, and new screening technologies, including liquid-based cytology and HPV DNA testing
BWH (2004)	• To provide physicians with clear guidelines for cervical cancer screening
PEBC (2005) New	• To identify the optimal cervical screening tool (conventional cytology, liquid based cytology, or HPV DNA testing) • To evaluate whether organized cervical screening programs with recall mechanisms reduce the incidence of and mortality due to cervical cancer compared to spontaneous cervical screening • To identify the most appropriate time for initiation and cessation of cervical screening • To identify the time interval at which women should be screened • To identify whether women in special circumstances should be screened (i.e., pregnant women, women post-hysterectomy, HIV positive women, women who have sex with women) • To identify the optimal management for women with abnormal cytology (up to but not including colposcopy/HPV management)
UMHS (2004)	• To implement an evidenced-based strategy for cancer screening in adults
USPSTF (2003)	• To summarize the current USPSTF recommendations on screening for cervical cancer and the supporting evidence • To update the 1996 recommendations contained in the Guide to Clinical Preventive Services, Second Edition
Target Population	
ACS (2002)	• Women in the United States • Women and female adolescents beginning approximately three years after the onset of vaginal intercourse, no later than 21 years of age

	• Women who have had a total hysterectomy
BWH (2004)	• Women in the United States • Women who are sexually active, starting within three years after onset of sexual activity • Women over 21 years of age
PEBC (2005) New	• Women in Ontario, Canada • All women who are, or have ever been, sexually active
UMHS (2004)	Cervical Cancer Screening Recommendations • Women in the United States • Women starting within 3 years after onset of vaginal intercourse • Women age 21 and older • Women who have undergone a total hysterectomy
USPSTF (2003)	• Women in the United States • Women who have been sexually active and have a cervix • Women older than age 65 • Women who have had a total hysterectomy for benign disease
Intended Users	
ACS (2002)	Advanced Practice Nurses; Allied Health Personnel; Health Care Providers; Health Plans; Hospitals; Managed Care Organizations; Nurses; Patients; Physician Assistants; Physicians; Public Health Departments
BWH (2004)	Physicians
PEBC (2005) New	Physicians
UMHS (2004)	Physicians
USPSTF (2003)	Physicians
Screening Interventions Considered	

ACS (2002)	1. Cervical cancer screening, including whom to test, when to initiate and discontinue testing, and screening interval 2. Screening following hysterectomy 3. Screening tests • Papanicolaou (Pap) test • Liquid-based Pap technology (ThinPrep®) • HPV DNA testing with cytology 4. Additional screening considerations such as, patient counseling/education Note: Additional topics are considered in the guideline but not addressed in this synthesis, including pelvic and rectal exams, referral for women with low-grade lesions, health insurance/coverage issues, and methods for collecting cervical cytology samples.
BWH (2004)	1. Cervical cancer screening, including whom to test, when to initiate and discontinue testing, and screening interval 2. Screening following hysterectomy 3. Screening tests • Papanicolaou (Pap) test • Liquid-based Pap technology (ThinPrep®, SurePath®) • HPV DNA testing with cytology Note: Additional topics are discussed in the guideline but not addressed in this synthesis, including methods for performing the Pap test, interpretation of Pap smear results (Bethesda system); screening follow-up, tracking, and reporting results; and appropriate responses to results (e.g., repeat Pap test, colposcopy, HPV testing).
PEBC (2005) New	1. Cervical cancer screening, including whom to test, when to initiate and discontinue testing, and screening interval 2. Screening after hysterectomy 3. Screening women with special circumstances 4. Screening tests • Liquid-based cytology (ThinPrep®, SurePath®) • Conventional smear cytology • HPV DNA testing with cytology Note: This guideline also makes recommendations concerning a province-wide screening program with a recall mechanism and management of abnormal cytology.
UMHS (2004)	1. Cervical cancer screening, including whom to test, when to initiate and discontinue testing, and screening interval 2. Screening following hysterectomy 3. Screening tests • Papanicolaou (Pap) test • Liquid-based Pap technology (ThinPrep®) • Computerized rescreening of negative smears (Auto Pap 300) (optional adjunct to manual reading) • HPV DNA testing with cytology 4. Additional screening considerations, such as patient counseling/education Note: Additional topics are considered in the guideline but not addressed in this synthesis, including the role of screening pelvic exam alone. This guideline also

	addresses screening for breast cancer, colorectal cancer, and prostate cancer. These topics are addressed in other guideline syntheses.
USPSTF (2003)	1. Cervical cancer screening, including whom to test, when to initiate and discontinue testing, and screening interval 2. Screening following hysterectomy 3. Screening tests • Papanicolaou (Pap) test • Routine use of new technologies to screen for cervical cancer • Thin layer cytology (ThinPrep®, AutoCyte PREP®) • Computerized rescreening (PapNet®) • Algorithm-based screening (AuroPap®) • Routine use of HPV testing as a primary screening test for cervical cancer

TABLE 2: COMPARISON OF RECOMMENDATIONS FOR CERVICAL CANCER SCREENING

Whom To Test (Including when to initiate and discontinue)	
ACS (2002)	When to Start Screening Cervical cancer screening should begin approximately three years after the onset of vaginal intercourse. Screening should begin no later than 21 years of age. It is critical that adolescents who may not need a cervical cytology test obtain appropriate preventive health care, including assessment of health risks, contraception, and prevention counseling, screening, and treatment of sexually transmitted diseases. The need for cervical cancer screening should not be the basis for the onset of gynecologic care. When to Discontinue Screening Women who are age 70 and older with an intact cervix and who have had three or more documented, consecutive, technically satisfactory normal/negative cervical cytology tests, and no abnormal/positive cytology tests within the 10-year period prior to age 70 may elect to cease cervical cancer screening. Screening is recommended for women who have not been previously screened, women for whom information about previous screening is unavailable, and for whom past screening is unlikely. Women who have a history of cervical cancer, in utero exposure to DES, and/or who are immunocompromised (including HIV+) should continue cervical cancer screening for as long as they are in reasonably good health and do not have a life-limiting chronic

	condition. Until more data are available, women aged 70 and older who have tested positive for HPV DNA should continue screening at the discretion of their health care provider. Women over the age of 70 should discuss their need for cervical cancer screening with their health care provider based on their individual circumstances (including the potential benefits, harms, and limitations of screening) and make informed decisions about whether to continue screening. Women with severe comorbid or life-threatening illnesses may forego cervical cancer screening.
BWH (2004)	Whom to Test • All women who are sexually active, starting within three years after onset of sexual activity • All women over 21 years of age • Older women: The American Cancer Society and the Society for Gynecologic Oncologists recommend that cervical cancer screening be discontinued in women over age 70 if they have had regular previous screenings with three normal Pap test results, and no abnormal tests in the previous 10 years. The USPSTF recommends stopping at age 65 for women who have been regularly screened and have had consistently normal results. Nonetheless, women still need annual gynecologic histories and pelvic exams since the majority of other gynecologic cancers occur in this age group. Note: Women of any age who have a new sexual partner may have had a new exposure to HPV infection. Clinicians may consider continuing annual Pap smears in these women, although there are not data at this time to support this practice.
PEBC (2005) New	Screening Initiation Cervical cytology screening should be initiated within three years of first vaginal sexual activity (i.e., vaginal intercourse, vaginal/oral, and/or vaginal/digital sexual activity) (C-III). Screening Cessation Screening may be discontinued after the age of 70 if there is an adequate negative screening history in the previous 10 years (i.e., 3 to 4 negative tests) (B-II).
UMHS (2004)	• Initiate. Start within 3 years after onset of vaginal intercourse [B] or at age 21 for women who are not sexually active [D]. Women who have undergone a total hysterectomy do not require screening unless the hysterectomy was performed because of cervical cancer or its precursors [C]. • Terminate. Screening may be discontinued in women past age 65 (as recommended by the USPSTF) or age 70 (as recommended by the ACS and the NCCN) who have at least three normal or negative smears in the past 10 years and no previous history of

	cervical abnormality [C].
USPSTF (2003)	• The USPSTF strongly recommends screening for cervical cancer in women who have been sexually active and have a cervix. A recommendation. The USPSTF found good evidence from multiple observational studies that screening with cervical cytology (Pap smears) reduces incidence of and mortality from cervical cancer. Direct evidence to determine the optimal starting and stopping age and interval for screening is limited. Indirect evidence suggests most of the benefit can be obtained by beginning screening within 3 years of onset of sexual activity or age 21 (whichever comes first) and screening at least every 3 years (see Clinical Considerations below). The USPSTF concludes that the benefits of screening substantially outweigh potential harms. • The USPSTF recommends against routinely screening women older than age 65 for cervical cancer if they have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer (see Clinical Considerations below). D recommendation. The USPSTF found limited evidence to determine the benefits of continued screening in women older than 65. The yield of screening is low in previously screened women older than 65 due to the declining incidence of high-grade cervical lesions after middle age. There is fair evidence that screening women older than 65 is associated with an increased risk for potential harms, including false-positive results and invasive procedures. The USPSTF concludes that the potential harms of screening are likely to exceed benefits among older women who have had normal results previously and who are not otherwise at high risk for cervical cancer. Clinical Considerations • The optimal age to begin screening is unknown. Data on natural history of HPV infection and the incidence of high-grade lesions and cervical cancer suggest that screening can safely be delayed until 3 years after onset of sexual activity or until age 21, whichever comes first. Although there is little value in screening women who have never been sexually active, many U.S. organizations recommend routine screening by age 18 or 21 for all women, based on the generally high prevalence of sexual activity by that age in the U.S. and concerns that clinicians may not always obtain accurate sexual histories. • Discontinuation of cervical cancer screening in older women is appropriate, provided women have had adequate recent screening

	with normal Pap results. The optimal age to discontinue screening is not clear, but risk of cervical cancer and yield of screening decline steadily through middle age. The USPSTF found evidence that yield of screening was low in previously screened women after age 65. New ACS recommendations suggest stopping cervical cancer screening at age 70. Screening is recommended in older women who have not been previously screened, when information about previous screening is unavailable, or when screening is unlikely to have occurred in the past (e.g., among women from countries without screening programs). Evidence is limited to define "adequate recent screening." The ACS guidelines recommend that older women who have had three or more documented, consecutive, technically satisfactory normal/negative cervical cytology tests, and who have had no abnormal/positive cytology tests within the last 10 years, can safely stop screening. • A majority of cases of invasive cervical cancer occur in women who are not adequately screened. Clinicians, hospitals, and health plans should develop systems to identify and screen the subgroup of women who have had no screening or who have had inadequate past screening.
Screening After Hysterectomy	
ACS (2002)	Screening with vaginal cytology tests following total hysterectomy (with removal of the cervix) for benign gynecologic disease is not indicated. Efforts should be made to confirm and/or document via physical exam and review of the pathology report (when available) that the hysterectomy was performed for benign reasons (the presence of CIN2/3 is not considered benign) and that the cervix was completely removed. Women who have had a subtotal hysterectomy should continue cervical cancer screening as per current guidelines. Women with a history of CIN2/3 or for whom it is not possible to document the absence of CIN2/3 prior to/or as the indication for the hysterectomy should be screened until three documented, consecutive, technically satisfactory normal/negative cervical cytology tests and no abnormal/positive cytology tests within a 10-year period are achieved. Women with a history of in utero DES exposure and/or with a history of cervical carcinoma should continue screening after hysterectomy for as long as they are in reasonably good health and do not have a life-limiting chronic condition.
BWH (2004)	Meta-analyses suggest that there is no benefit to performing Pap tests on women who have had a hysterectomy for a benign cause, have no cervix, and have no history of vaginal or cervical neoplasia. Because mortality from cervical cancer is highest in women over the age of 65, and because of the difficulties in obtaining a reliable history and/or old records, caution should be used before terminating screening in these patients. Note that, although a patient may not need a Pap test, the pelvic examination is an important part of the annual examination and may be important in identifying ovarian or vaginal lesions, or bladder

	prolapse. Women who have had a hysterectomy should continue to have Pap under the following circumstances: • A history of HSIL prior to hysterectomy: obtain Pap tests every two to three years until 65 to 70 years old, then discontinue screening if three negative/normal Paps • Inadequate records regarding the reason for hysterectomy or results of previous Pap tests
PEBC (2005) New	• Screening can be discontinued in women who have undergone total hysterectomy for benign causes with no history of cervical dysplasia or human papillomavirus (C-III). • Women who have undergone subtotal hysterectomy (with an intact cervix) should continue screening according to the guidelines.
UMHS (2004)	• Women who have undergone a total hysterectomy do not require screening unless the hysterectomy was performed because of cervical cancer or its precursors [C]. Clinical Background. Women who have undergone a total hysterectomy (with removal of the cervix) for benign gynecologic disease do not need to undergo screening with vaginal cytology. However, a health care provider should confirm and/or document via physical exam and review of the pathology report (when available) that the cervix was completely removed. Women who have had a subtotal hysterectomy should continue cervical cancer screening as per current guidelines.
USPSTF (2003)	• The USPSTF recommends against routine Pap smear screening in women who have had a total hysterectomy for benign disease. D recommendation. The USPSTF found fair evidence that the yield of cytologic screening is very low in women after hysterectomy and poor evidence that screening to detect vaginal cancer improves health outcomes. The USPSTF concludes that potential harms of continued screening after hysterectomy are likely to exceed benefits. Clinical Considerations • Discontinuation of cytological screening after total hysterectomy for benign disease (e.g., no evidence of cervical neoplasia or cancer) is appropriate given the low yield of screening and the potential harms from false-positive results in this population.

	Clinicians should confirm that a total hysterectomy was performed (through surgical records or inspecting for absence of a cervix); screening may be appropriate when the indications for hysterectomy are uncertain. ACS and ACOG recommend continuing cytologic screening after hysterectomy for women with a history of invasive cervical cancer or DES exposure due to increased risk for vaginal neoplasms, but data on the yield of such screening are sparse.
Screening Modality and Frequency	
ACS (2002)	Screening Interval and Modality After initiation of screening, cervical screening should be performed annually with conventional cervical cytology smears OR every two years using liquid-based cytology; at or after age 30, women who have had three consecutive, technically satisfactory normal/negative cytology results may be screened every two to three years (unless they have a history of in utero DES exposure, are HIV+, or are immunocompromised by organ transplantation, chemotherapy, or chronic corticosteroid treatment).

BWH (2004)	Modality
	
	Evidence-based data indicate that both liquid-based and conventional Pap tests are acceptable methods for preparing slides for cervical cancer screening
	
	Testing Frequency
	
	• Adolescents to age 30: Adolescents may not be forthcoming about when they start sexual activity. In addition, patients in this age group are at higher risk for sexually transmitted disease and pregnancy. Because of all of these concerns, providers should have a low threshold for performing Pap tests and pelvic exams in this age group. Screening should at least begin within three years after the initiation of sexual intercourse, but no later than age 21. Women should have a Pap test every year until age 30.
	• Women over age 30, low risk: After age 30, women who have had three consecutive satisfactory and normal/negative Pap tests may be screened every two to three years if they do not have any of the following:
	  • History of LSIL or HSIL (or CIN 2 or 3)
	  • A compromised immune system
	  • HIV infection
	  • Exposure to DES in utero
	
	More frequent screening at the provider's recommendation, or the

	patient's request, is also acceptable.
	
	• Women over age 30 with previous abnormal Pap tests: Women over 30 years of age who have not had three consecutive satisfactory normal/negative Pap smears should continue to have Pap tests every one to two years, as they did before age 30. Women treated for LSIL or HSIL who have completed the appropriate post-treatment follow-up should be screened annually until at least three consecutive negative Pap results have been documented. Women who have had a hysterectomy and have a history of LSIL/HSIL (CIN2/3) should have Pap tests annually until three normal tests are documented, and then every two to three years thereafter.
	• Women over age 30, higher risk: The following are co-factors for the development of intra-epithelial neoplasia. Therefore, if these are present, screening should be performed annually:
	  • DES exposure
	  • Prior abnormal Pap
	  • Immune suppression (immunosuppressive illnesses or drugs, renal transplantation, HIV)
	  • History of high-risk HPV type
	  • Current smoking status

PEBC (2005)
New
	Optimal Cervical Screening Tool
	
	• Liquid-based cytology is the preferred tool for cervical cytology screening (B-II). Conventional smear cytology remains an acceptable alternative (C-III).
	
	Screening Interval
	
	• Screening should be done annually until there are three consecutive negative Pap tests (C-III).
	• Screening should continue every two to three years after three annual negative Pap tests (B-II).
	  • Screening at a three-year interval is recommended, supported by an adequate recall mechanism (B-II).
	  • Women who have not been screened in more than five years should be screened annually until there are three consecutive negative Pap tests (C-III).
	
	Note: These recommendations do not apply to women who have had previous abnormal Pap tests. See management of abnormal cytology section in original guideline document for further information.
	
	Women with Special Circumstances
	
	• Immunocompromised or HIV positive women should receive annual screening (C-III).
	  • Examples of situations where women may be

	immunocompromised include women who have received transplants and women who have undergone chemotherapy. • Indications for screening frequency for pregnant women should be the same as women who are not pregnant (B-III). Manufacturer's recommendations for the use of individual screening tools in pregnancy should be taken into consideration. • Women who have sex with women should follow the same cervical screening regimen as women who have sex with men (B-II).
UMHS (2004)	Modality Pap smear of cervical cells or liquid based cervical cytology (ThinPrep®). Frequency • Low risk. Annually with conventional Pap smears or every two years using the ThinPrep until age 30. Starting at age 30, women who have had three consecutive technically satisfactory normal or negative cytology results may be screened every two to three years [C]. ("Low risk" includes women who do not have a history of in utero exposure to DES, are not immunocompromised or HIV+, and have had three consecutive normal or negative cytology results.) • High risk. Screen annually [D].
USPSTF (2003)	• The U.S. Preventive Services Task Force (USPSTF) strongly recommends screening for cervical cancer in women who have been sexually active and have a cervix. A recommendation. The USPSTF found good evidence from multiple observational studies that screening with cervical cytology (Pap smears) reduces incidence of and mortality from cervical cancer. Direct evidence to determine the optimal starting and stopping age and interval for screening is limited. Indirect evidence suggests most of the benefit can be obtained by beginning screening within 3 years of onset of sexual activity or age 21 (whichever comes first) and screening at least every 3 years (see Clinical Considerations below). The USPSTF concludes that the benefits of screening substantially outweigh potential harms. Clinical Considerations • The USPSTF found no direct evidence that annual screening achieves better outcomes than screening every 3 years. Modeling studies suggest little added benefit of more frequent screening for most women. The majority of cervical cancers in the U.S. occur in

	women who have never been screened or who have not been screened within the past 5 years; additional cases occur in women who do not receive appropriate follow-up after an abnormal Pap smear. Because sensitivity of a single Pap test for high-grade lesions may only be 60% to 80%, however, most organizations in the U.S. recommend that annual Pap smears be performed until a specified number (usually 2 or 3) are cytologically normal before lengthening the screening interval. The ACS guidelines suggest waiting until age 30 before lengthening the screening interval; ACOG identifies additional risk factors that might justify annual screening, including a history of cervical neoplasia, infection with HPV or other STDs, or high-risk sexual behavior, but data are limited to determine the benefits of these strategies.
New Technologies (Liquid-based Pap Technology; Other)	
ACS (2002)	Liquid-based Pap Technology As an alternative to conventional cervical cytology smears, cervical screening may be performed every two years using liquid-based cytology; at or after age 30, women who have had three consecutive, technically satisfactory normal/negative cytology results may be screened every two to three years (unless they have a history of in utero DES exposure, are HIV+, or are immunocompromised).
BWH (2004)	Liquid-based Pap Technology Liquid based Pap tests (ThinPrep®, SurePath®) have been available for several years. One of these (ThinPrep®) is now commonly used at BWH. Slides prepared from liquid based Pap tests contain less blood and fewer thick cell clumps. The test has higher sensitivity for detecting LSIL and HSIL and a higher rate of satisfactory specimens than the conventional Pap smear. This test has been approved by the FDA as a replacement for the traditional Pap test. A liquid-based Pap test costs approximately $12 more than a conventional Pap test and is covered by most insurers. An additional benefit to using the liquid-based Pap test is that if the test returns with the result "Atypical Squamous Cells--Unknown Significance (ASC-US)", the residual liquid from the test can be used to run a DNA test for high-risk HPV types.
PEBC (2005) New	Liquid-based Pap Technology Liquid-based cytology (LBC) is the preferred tool for cervical cytology screening (B-II). Conventional smear cytology remains an acceptable alternative (C-III).

UMHS (2004)	Liquid Based Pap Technology UMHS finds that the ThinPrep® LPB system collects more cells, leads to better quality slides, and is both more sensitive and specific than the Pap smear. Other UMHS notes that the FDA has approved a computerized device (AutoPap 300) as an adjunct to manual screening. The system is used to rescreen negative smears and approximately 10% to 20% of slides are classified as abnormal using a computerized cellular analysis. These slides are then reviewed by a pathologist.
USPSTF (2003)	• The USPSTF concludes that the evidence is insufficient to recommend for or against the routine use of new technologies to screen for cervical cancer. I recommendation. The USPSTF found poor evidence to determine whether new technologies, such as liquid-based cytology, computerized rescreening, and algorithm based screening, are more effective than conventional Pap smear screening in reducing incidence of or mortality from invasive cervical cancer. Evidence to determine both sensitivity and specificity of new screening technologies is limited. As a result, the USPSTF concludes that it cannot determine whether the potential benefits of new screening devices relative to conventional Pap tests are sufficient to justify a possible increase in potential harms or costs.
HPV DNA Testing With Cytology	
ACS (2002)	Preliminary Recommendation. At the time of the development of this guideline, HPV DNA testing with cytology for primary cervical cancer screening had not been approved by the FDA. Based on the available data, both published and unpublished, the ACS guideline review panel found this technology to be promising. Should the FDA approve HPV DNA testing for this purpose, it would be reasonable to consider that for women aged 30 and over, as an alternative to cervical cytology testing alone, cervical screening may be performed every three years using conventional or liquid-based cytology combined with a test for DNA from high-risk HPV types. Frequency of combined cytology and HPV DNA testing should NOT be more often than every three years. Counseling and education related to HPV infection is a critical need. Consensus guidelines for the management of women with a technically satisfactory normal/negative cytology result and a HPV DNA test result that is positive for high-risk HPV types would need to be developed. NGC note: FDA approved a combined cervical cytology/HPV test March 31, 2003.

BWH (2004)	In women aged 30 or over, the FDA has recently approved a combined Pap/HPV DNA test for primary screening. If a patient has the combined screen and tests negative, the screening interval should then be extended to three years. More frequent screening with the Pap/HPV combined test is not cost effective. The risk of cervical pre-cancer or cancer with less frequent screening, however, approaches that of no screening. Therefore, a clinician should opt for combined Pap/HPV screening only in the most compliant patients and if an excellent patient tracking system is in place. At the present time, the Pap/HPV screening option is not available at BWH.

PEBC (2005) New	HPV DNA Testing as a Primary Screening Tool
	
	The evidence supporting the use of HPV DNA testing as a primary screening tool as compared to conventional cytology indicates that HPV testing is more sensitive, but less specific than conventional cytology. The information regarding HPV screening continues to evolve but presently the two technology assessments (reviewed by the guideline developers) that examined HPV testing indicated that it should not be routinely recommended as a primary screening test. In the future HPV screening, especially in women over the age of 30, may prove useful but further data in the Ontario context is needed.
	
	HPV DNA Testing in Women with ASC-US
	
	• HPV DNA testing with cytology is recommended for women aged 30 or older with ASC-US (C-III).
	  • If the HPV DNA test is positive, women should be referred for colposcopy. If the HPV DNA test is negative, women should have repeat cytology in 12 months. Once a woman has had two negative cytology test results, she should return to routine screening.
	  • In the absence of HPV DNA testing, a repeat Pap test in six months is acceptable. If the Pap test is abnormal, women should be referred for colposcopy. If the Pap test is negative, women should have repeat cytology in another six months. Once a woman has had two negative Pap test results, she should return to routine screening.

UMHS (2004)	While routine testing on all patients for human HPV has been proposed as an alternative screening test, the high prevalence of HPV in young women and low positive predictive value for higher-grade lesions limits its usefulness. At the University of Michigan, HPV testing for high risk subtypes is currently performed on the ThinPrep samples from patients with an ASC-US pap smear. If positive for high-risk subtypes, these patients should be referred for colposcopy. If negative for high-risk HPV subtypes, the women may be followed with a repeat Pap smear in one

	year, based on the negative predictive value of our current HPV test being 98%.
USPSTF (2003)	• The USPSTF concludes that the evidence is insufficient to recommend for or against the routine use of HPV testing as a primary screening test for cervical cancer. I recommendation. The USPSTF found poor evidence to determine the benefits and potential harms of HPV screening as an adjunct or alternative to regular Pap smear screening. Trials are underway that should soon clarify the role of HPV testing in cervical cancer screening. HPV Testing in Women with ASC-US Liquid-based cytology permits testing of specimens for HPV, which may be useful in guiding management of women whose Pap smear reveals atypical squamous cells.
Patient Education/Counseling	
ACS (2002)	ACS and others should educate women, particularly teens and young women, that a pelvic exam does not equate with a cytology (Pap) test, and that women who may not need a cytology test still need regular health care visits, including gynecologic care and STD screening and prevention.
BWH (2004)	No recommendations offered
PEBC (2005) New	No recommendations offered
UMHS (2004)	It is important that women who may not need a cervical cytology test obtain appropriate preventive health care, including contraception and prevention counseling, and screening and treatment of sexually transmitted diseases.
USPSTF (2003)	No recommendations offered

TABLE 3: BENEFITS AND HARMS
Benefits

ACS (2002)	Reductions in Cancer Incidence and Mortality Cervical cancer mortality in the United States has decreased over the last five decades by over 70 percent, in large part attributable to the introduction of the Papanicolaou (Pap) test. Cervical cancer, once the number one cancer killer of women, now ranks 13th in cancer deaths for women in the United States. As cervical cytology screening has become more prevalent, preinvasive lesions of the cervix are detected far more frequently than invasive cancers. Women with preinvasive lesions have a five-year survival rate of nearly 100 percent. When cervical cancers are detected at an early stage, the five-year survival rate is approximately 92 percent. The purpose of screening, in addition to detecting cervical cancers at an early stage, is to detect and remove high-grade lesions and thus prevent potential progression to cervical carcinoma.
BWH (2004)	Reductions in Cancer Incidence and Mortality The incidence of and mortality from cervical cancer in the United States has decreased steadily over the past 40 years primarily due to Pap test screenings. Quality of Care The recommendations presented are designed to provide women with optimal and personalized care.
PEBC (2005) New	• Optimal use of cervical screening tools • Reduced incidence and mortality due to cervical cancer • Appropriate initiation, intervals, and cessation of cervical screening • Optimal management of women with abnormal cytology
UMHS (2004)	Reductions in Cancer Incidence and Mortality Correlational studies show significant declines in both the incidence of cervical cancer and cervical cancer mortality rates in North American and western Europe following the introduction of screening programs. The reduction in mortality correlated closely with the intensity of the screening. Case control studies support the correlational data and show a decrease in the incidence of invasive cancer by 60 to 90%. Increased frequency of screening is associated with a greater reduction in rate of cervical cancer.
USPSTF (2003)	Reductions in Cancer Incidence and Mortality Detection of cervical cancer in its earliest stages is lifesaving, as survival of cancer of the cervix uteri depends heavily on stage at diagnosis. Although 92 percent of women will survive 5 years when the

	cancer is localized, only 13 percent will survive distant disease. Introduction of screening programs to populations naive to screening reduces cervical cancer rates by 60-90 percent within 3 years of implementation. This reduction of mortality and morbidity with introduction of the Pap test is consistent and dramatic across populations. Although no prospective trial of Pap screening has ever been conducted, correlational studies of cervical cancer trends in countries in North America and Europe demonstrate dramatic reductions in incidence of invasive cervical cancer and a 20-60 percent reduction in cervical cancer mortality.
Harms	
ACS (2002)	• False-negative results occur even in optimized screening programs and cannot be entirely eliminated. • There is evidence that screening is associated with potential harms, including anxiety and discomfort during cytology sampling of some older women, and the invasive procedures, anxiety, and higher health care costs due to false-positive cytology results.
BWH (2004)	There is a significant false-negative rate in Pap test results -- at least 20 percent -- meaning that one out of five women who have a significant lesion will have a negative Pap test.
PEBC (2005) New	None stated
UMHS (2004)	None stated
USPSTF (2003)	• The USPSTF concludes that the potential harms of screening are likely to exceed benefits among older women who have had normal results previously and who are not otherwise at high risk for cervical cancer. • The USPSTF concludes that potential harms of continued screening after hysterectomy are likely to exceed benefits. • The USPSTF concludes that it cannot determine whether the potential benefits of new screening devices relative to conventional Pap tests are sufficient to justify a possible increase in potential harms or costs. The USPSTF did not identify studies that specifically addressed harms of new technologies for cervical cancer screening. Better data on the performance characteristics (sensitivity, specificity, and predictive values) of the new screening technologies are needed to determine the risk for harm to an individual patient. Although the data are limited, on average these tools improve sensitivity and reduce specificity. This finding suggests that increased detection of low-grade lesions and false positives are the primary potential sources of harm; i.e., harm

	may take the form of increased evaluations, including repeated Pap tests and biopsies; possible unnecessary treatment for low-grade lesions; and psychological distress for the women diagnosed with low grade lesions that may not have been clinically important. These harms are poorly documented for conventional Pap testing and have not yet been assessed for new technologies. • With regard to HPV testing, the USPSTF did not identify any studies that quantified harms. Potential harms commented on in the literature include stigma, partner discord, adverse effects of labeling some women as being at high risk for cervical cancer, and the potential undermining of routine cytologic screening known to be effective.

TABLE 4: EVIDENCE RATING SCHEMES AND REFERENCES	
ACS (2002)	Criteria for Evidence Grading Strong Evidence Evidence is useful to the panel's task (reviewer's conclusion may be different from authors'). Sample size is adequate to give statistical power. Unbiased or biases addressed. Endpoint defined as cervical intraepithelial neoplasia 2/3 (CIN2/3). Limited Evidence Conclusions/assumptions are not supported by data, but some useful data is provided. Sample size insufficient to give statistical power to observe a true effect. Flaws or biases that could negate conclusions. Study design weakens conclusions (reviewer should provide explanation). Review article with a new perspective. No Evidence/Exclude No relevant data (e.g., review article). Symptomatic women. Shortcomings negate conclusions. Articles not in English.

PEBC (2005) New	Quality of Evidence I: Evidence from at least 1 randomized controlled trial II: Evidence from at least 1 clinical trial without randomization, from cohort or case-controlled analytic studies, or from multiple time series studies or dramatic results from uncontrolled experiments III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees Strength of Recommendation A: Good evidence for efficacy and substantial clinical benefit support recommendation for use. B: Moderate evidence for efficacy or only limited clinical benefit support recommendation for use. C: Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds. D: Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. E: Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use.
UMHS (2004)	Levels of evidence reflect the best available literature in support of an intervention or test: A = randomized controlled trials B = controlled trials, no randomization C = observational trials D = opinion of expert panel
USPSTF (2003)	Quality of Evidence The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor): Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes. Fair: Evidence is sufficient to determine effects on health outcomes,

	but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes. Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes. Strength of Recommendations The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms). A. The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms. B. The USPSTF recommends that clinicians provide [this service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms. C. The USPSTF makes no recommendation for or against routine provision of [the service]. The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation. D. The USPSTF recommends against routinely providing [the service] to asymptomatic patients. The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits. I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.

GUIDELINE CONTENT COMPARISON

The American Cancer Society (ACS), Brigham and Women's Hospital (BWH), the Program in Evidence-based Care (PEBC), the University of Michigan Health System (UMHS), and the United States Preventive Services Task Force (USPSTF) present recommendations for cervical cancer screening. PEBC, UMHS, and USPSTF rank the level of evidence for each major recommendation. ACS, PEBC, UMHS,

and USPSTF provide, in narrative form, the explicit reasoning behind their judgments for all major recommendations, while BWH provides this for some recommendations.

The guidelines differ in scope. UMHS, for instance, in addition to its cervical cancer screening recommendations, presents recommendations for breast cancer, colorectal cancer, and prostate cancer screening (ACS and USPSTF provide recommendations for these other topics in separate guidelines). ACS and BWH consider methods for collecting the Pap smear sample; BWH also addresses Pap smear results, follow-up treatment, and tracking and reporting of screening results. ACS addresses patient referral, the need for pelvic and rectal exams, and health insurance. PEBC provides recommendations concerning management of women with abnormal cytology. Excepting the topic of HPV testing in screened women with abnormal cytology results, these additional topics are not included in this synthesis, which focuses on primary screening for cervical cancer.

Areas of Agreement

When to Initiate and Discontinue Screening

ACS, BWH, UMHS, and USPSTF are in agreement concerning when to initiate cervical screening, with all four groups recommending that screening be started within 3 years after the onset of vaginal intercourse, or by age 21. PEBC agrees that screening should be started with 3 years of onset of first vaginal sexual activity, but does not include an age criterion (see Areas of Differences below).

General agreement also exists among ACS, BWH, PEBC, UMHS, and USPSTF concerning when to stop screening. All five groups recommend that screening be discontinued in older women who have had adequate recent screening (i.e., at least three normal Pap smears within the prior 10 years) and who have no risk factors for cervical cancer. The five guidelines differ, however, concerning the precise age at which screening should be discontinued in older women; these differences are discussed below.

Screening Following Hysterectomy

ACS, BWH, PEBC, UMHS, and USPSTF agree that screening is not necessary in women who have had a total hysterectomy for benign gynecologic disease. However, these guidelines are in general agreement regarding the need to continue screening when there is inadequate documentation of the reason for the hysterectomy and/or when risk factors for cervical cancer are present (such as cervical dysplasia or HPV).

Patient Education

Both ACS and UMHS are in general agreement that women, particularly teens and young women, receive education about appropriate preventive health care, contraception, and prevention of sexually transmitted diseases. BWH, PEBC, and USPSTF do not address this topic.

Areas of Differences

Whom to Screen

PEBC differs from the other four guidelines in that it does not specify an age by which screening should be initiated; the other guidelines indicate screening should start within three years of onset of sexual activity or by age 21. The PEBC guideline developers chose not to include a specific age to initiate screening, citing lack of evidence to support a particular age over another. The guideline states that linking Pap testing to the initiation of vaginal sexual activity is also more practical than choosing a specific age. PEBC points out that Pap smear screening has evolved since the 1950's into a highly effective cancer prevention tool; this has occurred without randomized controlled trials, and the benefit of this test is so evident that trials involving withholding the test are unethical. Therefore, there is little evidence in the literature to indicate the optimal timing for the initiation and cessation of cervical screening. PEBC notes that previous cervical screening guidelines have made recommendations for the initiation and cessation of screening based on limited evidence, previous practice, and expert consensus.

The guidelines all recommend screening be initiated within 3 years of onset of sexual activity, but they differ in how sexual activity is defined. BWH and USPSTF use the most general term, recommending screening begin within three years of onset of "sexual activity." ACS and UMHS, however, use the more limited term "vaginal intercourse." PEBC recommends that screening begin within three years of "first vaginal sexual activity," which is defined as "vaginal intercourse, vaginal/oral and/or vaginal/digital sexual activity." PEBC justifies this recommendation by pointing out that it is recognized that vaginal transmission of HPV can occur with sexual activities other than intercourse, including vaginal/oral and/or vaginal/digital activity.

When to Discontinue Screening

Although, ACS, BWH, PEBC, UMHS, and USPSTF agree that screening can be discontinued in low-risk older women, the groups recommend different age cut-offs. ACS and PEBC recommend discontinuing screening at age 70, whereas USPSTF recommends stopping at age 65. USPSTF notes that it found limited evidence to determine the benefits of screening in women older than age 65, that screening women older than this is associated with an increased risk for potential harms (including false-positive results and invasive procedures), and that the potential harms are likely to exceed benefits. Both BWH and UMHS recommend that, for women who have previously undergone routine screening, screening be discontinued at either age 65 (citing USPSTF) or age 70 (citing ACS/NCCN). UMHS further adds that many women older than age 65 have never been screened or have been screened fewer than two times for cervical cancer and that these women would most likely benefit from continued screening efforts. BWH notes that older women who are no longer being screened still require annual pelvic exams and gynecologic histories. BWH further notes that women of any age who have a new sexual partner may have had a new exposure to HPV infection and clinicians may consider continuing annual Pap smears in these women, although there are no data at this time to support this practice. Concerning this difference in opinions as to whether screening should be discontinued at age 65 or at age 70, PEBC states that the literature regarding the cessation of cervical screening is sparse and problematic. Studies have often included women who had never been

screened with those who have had adequate screening histories, making an evaluation of the evidence difficult.

Screening Interval

The organizations also differ in their recommendations concerning the screening interval. ACS, BWH, and UMHS recommend that screening be done annually with conventional cytology or every 2 years with LBP technology until age 30. At that age, the screening interval can be lengthened to every 2 to 3 years (in women who have had three consecutive normal tests and are at low risk for cervical cancer). In contrast, USPSTF found no direct evidence that annual screening achieves better outcomes than screening every 3 years; it recommends screening be done (with conventional smears) at least every 3 years for all eligible women.

PEBC recommends screening be done annually until there are three consecutive negative Pap tests, and thereafter every 2-3 years; citing a 2003 study, PEBC recommends a 3-year interval if screening is supported by an adequate recall mechanism. According to the PEBC, there has been a move to lengthen the screening interval with the use of LBP technology under the assumption that the increase in sensitivity can offset the decreased screening frequency and lead to cost reductions associated with the more expensive LBP method. PEBC cautions that these predictions are largely based on modeling and have yet to be tested.

Conventional Cytology vs. Liquid-based Pap Cytology

Four of the five guidelines recommend both conventional and LBP technology. According to BWH, evidence-based data indicate that both tests are acceptable methods for cervical cancer screening. ACS states that LBP cytology is somewhat more sensitive but less specific for high-grade lesions. Similarly, UMHS finds that the ThinPrep® LPB system collects more cells, leads to better quality slides, and is both more sensitive and specific than the Pap smear. PEBC recommends LBP cytology as the preferred tool, although conventional smear technology is an acceptable alternative. In contrast to the other four guidelines, USPSTF found insufficient evidence to make a recommendation either for or against LBP technology, noting that evidence to determine the sensitivity and specificity of LBP cytology is limited, that no studies of LBP cytology have assessed cervical cancer outcomes, and that LBP cytology (ThinPrep®, AutoCyte PREP®) is cost-effective only if used at screening intervals of 3 years or longer.

The choice of screening technology impacts on the recommended screening interval. Both ACS and UMHS recommend that a longer screening interval be used with LBP cytology (i.e., at least every 2 years until age 30) than with conventional cytology (i.e., annually until age 30). ACS states that LBP cytology is somewhat more sensitive but less specific for high-grade lesions. Screening with LBP cytology at the same interval as conventional cytology is thus likely to result in significant increases in detection of ASC-US and low-grade abnormalities, leading to overtreatment and increased health care costs. PEBC also points out that the introduction of LBP technology will lead to increased costs that will have to be balanced with other screening efficiencies.

HPV DNA Testing With Cytology

All of the guidelines address use of HPV DNA testing as a primary screening tool for cervical cancer (i.e., performed on all women screened); three guidelines (BWH, UMHS, and PEBC) also address HPV DNA testing as a further assessment for the subset of women with ASC-US results from a Pap smear.

The guidelines differ somewhat regarding the issue of HPV DNA testing combined with conventional and/or liquid-based Pap cytology as a primary screening tool. The ACS and USPSTF guidelines were both released prior to FDA approval of this procedure. USPSTF found insufficient evidence to recommend for or against the routine use of HPV testing as a primary screening test for cervical cancer. ACS, on the other hand, offers a preliminary recommendation (should the FDA approve the procedure) for the use of HPV-DNA testing combined with conventional or liquid-based cytology in women aged 30 and over as an alternative to cervical cytology testing alone. ACS further adds that the frequency of combined cytology and HPV DNA testing should NOT be more often than every 3 years because it is not cost effective to do so. ACS' rationale for restricting screening with HPV DNA to women aged 30 and over is that this would reduce the number of women to be referred for colposcopy due to transient HPV infection. Screening more frequently than every 3 years would not significantly improve sensitivity, but would likely result in over-evaluation and potential overtreatment of many women for transient HPV infections.

The BWH, PEBC, and UMHS guidelines were developed after FDA approved a combined Pap/HPV DNA test for primary screening. BWH states that the combined test should not be done more often that every 3 years (in patients that test normal) because more frequent HPV/Pap testing is not cost effective. BWH further adds that this method should be reserved for only the most compliant patients, given that cancer or pre-cancer risk in patients undergoing less frequent screening approaches that of no screening. BWH does not currently offer HPV/Pap as a screening option for its patients. Similarly, UMHS does not use HPV/Pap for primary screening, noting that, while routine testing on all patients for HPV has been proposed as an alternative screening test, the high prevalence of HPV in young women and low positive predictive value for higher-grade lesions limits its usefulness. PEBC does not address use of the combined Pap/HPV test for primary screening.

Apart from use of HPV testing as a primary screening tool, BWI, PEBC, and UMHS do recommend HPV DNA testing on liquid from the Pap test for the subset of women with an ASC-US Pap smear result. USPSTF likewise notes that liquid-based cytology permits testing of specimens for HPV, which may be useful in guiding management of women with ASC-US Pap smear results. (NGC note: discussion of recommendations related to follow-up for abnormal Pap smear results are beyond the scope of this synthesis. See the original guideline documents for more information on this topic).

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